A Randomized Controlled Trial of a Weight Loss Maintenance Program in Adults with Obesity: The WLM3P Study

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Abstract

Background/Objectives:

Obesity, a chronic disease, requires effective strategies for weight loss (WL) and sustained maintenance. This study aimed to evaluate the effectiveness of the Weight Loss Maintenance 3 Phases Program (WLM3P) in achieving a clinically significant long-term WL (≥5% initial WL at 18 months) in adults with obesity compared to a standard low-carbohydrate diet (LCD).

Subjects/Methods:

In this two-phase trial, 112 participants targeting initial WL (0-6 months) and subsequent maintenance (7-18 months) were randomly assigned to either WLM3P or LCD groups.

Results: Of 112 randomized participants, 69% (n=77) completed the study. At 18 months, WL in the WLM3P group (n=40) was 15.5±8.3% compared to 9.6±8.5% in the LCD group (n=37) ($p<0.001$). The odds ratio of achieving WL≥10% and ≥15% were significantly higher in the WLM3P group at 18 months. Complete-case analysis revealed significantly greater improvements in BMI, body fat mass, visceral fat area, waist circumference, waist-to-hip ratio, HDL, and triglyceride/HDL ratio in WLM3P than in LCD. No serious adverse events were reported.

Conclusion: Both programs were effective in promoting clinically relevant WL and its maintenance. However, the WLM3P program was more successful in helping participants achieve greater WL targets of ≥10% and ≥15%, along with other clinical benefits, after an 18-month intervention. Trial registration number: NCT04192357.

1. Introduction

Obesity is an adiposity-based progressive and relapsing chronic disease with serious health implications[1]. It has been recognized as a major public health crisis worldwide [1]. More than half of the adult population in the Europe (53%) were considered overweight, 36% pre-obese, and 17% obese[2]. Portugal has a high obesity prevalence (16.4%) [3] and, according to the World Obesity Federation, that number will increase to 39% by 2035 [4].

Effective, affordable, and accessible obesity treatments are necessary for weight loss (WL) and maintenance. A successful intervention promotes and maintains a WL ≥ 5% from baseline for at least 1 year [5, 6]. This threshold of WL percentage has been identified as clinically meaningful based on improvements in metabolic health, including blood pressure, blood glucose, lipid profile, and psychological well-being. Expectedly, it has been observed that a greater WL leads to more significant disease-modifying effects [5–7]. Lifestyle interventions are associated with a WL of approximately 5–10% [5, 8], with a high percentage of poor responders [5–8] and a 30–50% regain of lost weight after 1-year post-treatment[9]. As part of the guidelines on obesity management for adults [5], clinicians may recommend

commercial weight management programs if they have evidence of safety and effectiveness. However, due to limited long-term data, clinical recommendations regarding these programs are still debated [5, 10]. Additionally, a systematic review and network meta-analysis conducted in 2021[11], which compiled 1-year outcomes of 14 popular WL programs, revealed that while most of them led to moderate WL within 6 months, only small differences were observed after 12 months, and the positive impact on cardiometabolic markers largely disappeared. Furthermore, adherence appears to be the main predictor of WL success, rather than specific dietary interventions [5, 6, 12]. Therefore, the most effective nutritional strategy for WL and maintenance remains to be determined, and an intensive and multicomponent approach can be crucial.

A carbohydrate-restricted/high-protein diet has become a popular strategy for WL and to prevent weight regain [13, 14]. According with Denning et al. [15], a low-carbohydrate diet (LCD) is defined as < 26% of Total Energy Intake from carbohydrate (%CTEI) and moderate carbohydrate diet 26–45% CTEI. High-protein diets contain > 25% of Total Energy Intake from protein (%PTEI) [16]. A carbohydrate-restricted/high-protein diet may improve body composition by increasing secretion of satiety hormones, lipolysis, thermic effect of proteins, glucose homeostasis, and promoting preservation of fat-free mass, which helps maintain resting energy expenditure despite WL [13, 17]. Evidence from studies with WL phases followed by weight-maintenance phases are limited and more research is needed to fully understand the long-term effects for WL [5, 6, 11]. Also, to optimize a high-protein diet, integrating specific high-protein foods can be beneficial for WL and satiety [18]. Recent research emphasizes the efficacy of time-restricted eating (TRE), a type of intermittent fasting based on the circadian rhythm, in both WL and treatment of metabolic disorders, revealing its role in weight management strategies [19, 20]. This chrononutrition-based dietary approach entails restricting eating to specific daily hours, incorporating fasting during the remaining period, with only water and unsweetened tea permitted[19, 20]. The incorporation of dietary supplements in a WL program may have the potential to work synergistically or additively to improve metabolic health outcomes through diverse mechanisms, including modulation of lipid and carbohydrate metabolism, appetite reduction via central nervous system interaction, influence on intestinal microbiota activity, and increased energy expenditure [21, 22]. Furthermore, digital platforms have been increasingly integrated into WL programs to improve adherence, track progress, and access resources that meet contemporary needs [23, 24]. In summary, weight management programs should be intensive and multicomponent interventions, including: 1) two active phases [WL phase (≥ 14 sessions in 6 months) to promote a clinically significant WL ≥ 5% and weight maintenance phase (≥ 1 year) focusing on sustaining WL], 2) individual or group counselling sessions; 3) negative energy balance; 4) nutritional recommendations, 5) physical activity advice; and 6) use of behavioral strategies [5–7]. Nutritional recommendations should consider the proportions and daily distribution of macronutrients, overall quantity, and quality of the diet (i.e. how much we eat and what we eat), as well as chrono-nutritional strategies, as TRE (i.e. when we eat)[19]. In addition, an effective weight management program must consider the individual's cardiometabolic risk factors, dietary preferences, long-term compliance, and weight regain prevention [5–7].

The Weight Loss Maintenance 3 Phases Program (WLM3P) is an innovative, highly structured, and intense lifestyle modification approach that integrates several evidence-based strategies to address obesity. This program comprises 7 key components: 1. dietary intervention with 3 phases (phases 1 and 2 for WL, a low carbohydrate/high protein energy-restriction diet, and phase 3 for weight maintenance, a moderate carbohydrate/high protein diet) [13, 14]; 2. one-to-one consultations [5–7]; 3. behavioral strategies [5–7], 4. TRE[19, 20] ; 5. dietary supplements [21, 22]; 6. high-protein specific food [18]; and a 7. mobile/web app [23]. The WLM3P aims to promote a clinically significant WL of 5%-10% during the initial two phases, with a follow-up phase 3 of at least one-year for long-term weight consolidation, in accordance with guidelines for obesity treatment [5, 6]. The novelty of this program is that it aggregates all these components to provide a comprehensive and holist approach to weight management, rather than evaluating the effectiveness of each one in isolation. Therefore, this study aimed to evaluate the effectiveness of the WLM3P in supporting patients to achieve a clinically significant WL ≥ 5% at 6 months and maintain this benchmark at 18 months compared to a standard LCD in adults with obesity.

2. Materials and Methods

2.1 Trial design

The WLM3P study was a randomized controlled trial, comprising 18 months (6-month WL period followed by a 12-month weight maintenance period) study conducted at NOVA Medical School, NOVA University of Lisbon, between March 2020 and January 2023. Participants were randomly allocated (1:1) to either WLM3P (n = 59) (intervention group) or LCD (n = 53) (active control group) (Fig. 1).

2.2 Participants

One hundred and twelve participants (18 to 65 years) with obesity [body mass index (BMI) of 30.0 to 39.9 kg/m^2] of both genders were recruited. Briefly, the key exclusion criteria were planned or current pregnancy, diabetes, previous or planned bariatric surgery, current participation in a WL program, or use of other treatments for obesity (ex. medications), severe disease (advanced organ failure, dementia, or cancer), active abuse of drugs or alcohol or inability to perform Inbody® (e.g., limb amputation) (Supplementary Table S1). The sample size calculation determined that 338 participants were needed to achieve an 80% power and a 5% error rate, assuming proportions of 50% and 35% in the intervention and control groups, respectively, achieving WL ≥ 5% at 18 months[7]. Considering a 32% attrition rate, recruitment aimed at 500 participants (250 per group) but ended prematurely due to lower-than-expected recruitment rates. Participants were randomly assigned by clinical research coordinators to either the intervention or control group using an automated computer-generated randomization scheme (sequentially numbered). The randomization process was controlled by the Principal Investigator, who was not involved in recruitment or intervention delivery. Once recruited, participants were blinded to the treatment allocation and a study identification number was assigned. None of the randomized participants included in the study received any financial or in-kind support. The study was approved by

the Ethics Committee of the NOVA Medical School (Lisbon, Portugal) (CEFCM Approval Number: 108/2018) and registered at www.clinicaltrials.gov (NCT04192357) before participants' recruitment. All participants provided written informed consent in accordance with the principles of the Declaration of Helsinki.

2.3 Dietary Interventions

In both groups, for WL period (months 0 to 6), dietary plans met 70% of participants' daily energy requirements (DER), and for weight maintenance period (months 6 to 18) 100% of participants' DER. Nutrition counseling (WL: 24 sessions in WLM3P, 6 sessions in LCD; weight maintenance: 12 sessions in both groups) provided clinical support, problem-solving, and maintenance efforts. In both interventions, participants were advised to eat more vegetables, avoid refined grains, sugar, trans fats, and focus on whole, nutrient-dense foods. Individual preferences were considered, and the meal preparation indications followed the Mediterranean diet principles. Physical activity counseling aimed for ≥ 150 minutes of moderate exercise per week (equivalent of ≥ 500 MET min/week)[5] for both groups. The descriptions of the dietary interventions are included in Additional file 1: Appendix 1.

2.3.1 WLM3P (Intervention Group)

The WLM3P is a structured nutritional and behavioral program based on 7 components:

1. Dietary intervention with 3 Phases (Phase 1 and Phase 2 – WL period, and Phase 3 – weight maintenance period). Phase 1 (1-month: low-carbohydrate (10–15% CTEI)/high-protein diet (35–45% PTEI); Phase 2 (5-month: low-carbohydrate (15–20% CTEI)/high-protein diet (30–40%PTEI); Phase 3 (12-month: moderate-carbohydrate (35–45% CTEI)/high-protein (25–30% CTEI) [15].
2. Regular one-to-one consultations [5–7]: During the WL period, participants had one-to-one weekly consultations (24 presential sessions) followed by a follow-up every month for 12-month (12 presential sessions).
3. Behavioral strategies [5–7, 25] with a particular emphasis on 4 pillars (nutrition education and meal planning, motivational support and goal setting, chrono-nutrition and physical activity) to provide personalized guidance, facilitate goal setting, and enable self-monitoring.
4. Time-restricted eating [19, 20]. For the WL phase, participants were instructed to choose the most suitable 10-hour window feeding for their schedule between 08:00 and 20:00 (fasting:eating of 14:10 hours) and 12:12 hours for the maintenance phase. In the fasting period, participants were only allowed to consume water, flavored carbonated water without sugar, unsweetened tea, and coffee.
5. Dietary supplements [21, 22]. A vitamin-mineral supplement, liver support, WL enhancer, and a diuretic were prescribed for 6 months as adjuncts to WL strategies.
6. High-protein specific food [18]. High protein pudding or drinks (2 per week) during WL period were used for satiety and appetite control.
7. Mobile and Web application[23].Weight loss and body composition progress, dietary plan prescriptions, and weekly goals were displayed with a Mobile and Web application to amplify

adherence to behavior changes.

In the WLM3P group, all dietary supplements and high-protein puddings/drinks were provided by the research team.

2.3.2. Active control group

Participants randomized to the control active group received a standard carbohydrate-restricted diet divided into two periods [(WL period (6-month: low-carbohydrate (≤ 26% CTEI) /high-protein diet (30–35% PTEI), and weight maintenance period (12-month: moderate-carbohydrate (< 45% CTEI)]/high-protein diet (25% PTEI)] [15]. During the 6-month WL period, participants had 6 in-person sessions, followed by a monthly follow-up for 12 months (12 in-person sessions).

Participants were provided with a detailed menu containing allowed and not-allowed foods and recipes to promote healthy food choices, which were designed to have a defined macronutrient distribution.

2.4. Outcomes

The primary endpoint was the percentage change in body weight and achievement of WL ≥ 5% from baseline to the 6 and 18-month time points. Secondary endpoints included the proportion of participants achieving weight reductions of at least 10%,15% or 20%, and the change from baseline to 6 and 18-month of the following variables: body composition [(body fat mass (BFM), skeletal muscle mass (SMM), visceral fat area (VFA) and waist-to-hip ratio (WHR), waist circumference)], metabolic profile [(Glucose, insulin, glycated hemoglobin (HbA1c), Homeostasis Model for Assessment (HOMA) (fasting insulin (uIU/mL) × fasting glucose (mg/dL)/405 [26]), low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides (TG), liver enzymes [plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT)], high sensitivity C-reactive protein (hsCRP), creatinine, vitamin D, magnesium, sodium, and potassium)], blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), dietary intake, physical activity, sleep time, fasting window, dropout rate, adherence rates, and adverse effects. Secondary outcomes related to changes in gut microbiota composition over time were also evaluated in this trial; however, this will be reported later.

2.4.1. Assessments

At baseline, socio-demographic and medical history were collected through a self-report questionnaire. Potential changes in medication were assessed during each visit.

Body composition was assessed monthly by bioelectrical impedance analysis (Inbody® model 770). Body mass index [(weight (kg)/height (m^2)] and skeletal muscle mass to visceral fat area ratio (S/V ratio) were calculated. Waist circumference (WC) was measured according to the protocol defined by the Directorate-General of Health [27]. At baseline, 6, and 18 months, the following measurements were performed: 1) fasting venous blood samples for biochemical analyses were determined by conducting

standard laboratory assays; 2) blood pressure was measured using a validated automatic device (OMRON HEM-7361T) according to the protocol defined by the Directorate-General of Health [28]; 3) dietary intake was calculated as an average of a 3 non-consecutive days food diary (two week days and one weekend day) and analyzed using the Portuguese Food Composition Table developed by the National Institute of Health Dr. Ricardo Jorge [29]; 4) physical activity, converted to Metabolic Equivalent Task minutes per week (MET-min/week), according to the International Physical Activity Questionnaire (IPAQ) scoring protocol [30]; 5) habitual sleep time, estimated by a questionnaire [(Habitual sleep time 'During weekdays: How many hours (and minutes) do you usually sleep?'; 'During weekend days: How many hours (and minutes) do you usually sleep?')) and a total weekly sleep score was calculated as: ((minutes Weekdays 5) + (minutes Weekend days 2))/7] [31]; and 6) fasting window determined by calculating the difference between the first and last episode of eating/drinking calorie-food/beverages. Therapeutic adherence was measured by the number of sessions attended [12]. In the WLM3P group, an evaluation of dietary supplement compliance was conducted using a 5-point Likert scale (0%, 25%, 50%, 75%, all). Adverse events were self-reported and assessed during each visit using a questionnaire, following the Good Clinical Practice and Health Research Authority processes [32]

2.5. Statistical analysis

Categorical variables are expressed as absolute (n) and relative (%) frequencies, while continuous variables are expressed as mean ± standard deviation or median and interquartile range [IQR, 25th-75th percentile]. Data were tested for normality by performing the Kolmogorov–Smirnov test and analyzing the distribution using histograms. A comparison of variables in the same group (baseline vs. follow-up) was performed using parametric tests (paired Student's t test) and nonparametric tests (Wilcoxon test) as appropriate, considering normality assumptions. For between-group comparisons (WLM3P vs. LCD), parametric tests (Student's t-test) and nonparametric tests (Mann-Whitney) were used as appropriate, considering normality assumptions. Hypotheses regarding categorical variables were tested using the chi-square test or Fisher's exact test, as appropriate. Logistic and linear regression models were carried out using each of the outcomes as dependent variables and as independent (explanatory) variables regarding the compared groups (intervention vs control (reference)), adjusted for age, sex, baseline body mass index, and baseline glucose (used since differences were observed at baseline) at 6 and 18 months. Coefficient regression (beta) and 95% confidence intervals (95% CI) are presented. The significance level used was 0.05. Statistical analysis was performed using the Statistical Package for the Social Sciences version 29.

3. Results

3.1. Participants characteristics

Among 216 adults with obesity screened for participation, a total of 112 individuals (mean age 45 ± 8.7 years) with a BMI of 34 ± 2.4 kg/m^2 and a body weight of 95.5 ± 11.6 kg was enrolled in the study. The majority of participants were Caucasian (98.2%), female (72.3%), married (43.8%), and college-educated

(79.5%). Participants were randomly assigned to either WLM3P group (n = 59) or LCD group (n = 53). A total of 77 participants (69%) completed the study (Fig. 1). Comorbid conditions, common among these patients, included hypertension (17%), depression/anxiety (15.2%), osteoarticular disorder (8.9%), and treated dyslipidemia (5.4%) (Table 1). No significant differences in baseline characteristics were observed between the two groups, except for fasting glucose (WLM3P group, 83.0 ± 8.6 mg/dL vs. LCD group, 88.1 ± 10.3 mg/dL; p = 0.008) (Table 1).

Table 1
Baseline characteristics of study participants.

Characteristics	WLM3P Group (n = 59)	LCD Group (n = 53)	p-value[1]
Demographics			
Age (years)	44.0 ± 8.8	46.2 ± 8.4	0.176
Sex, n (%)			
Female	42 (71.2)	39 (73.6)	0.777
Male	17 (28.8)	14 (26.4)	
Metabolic Conditions, n (%)			
Hypertension	7 (11.9)	12 (22.6)	0.129
Hypothyroidism	2 (3.4)	1 (1.9)	0.623
Dyslipidemia	3 (5.1)	3 (5.7)	0.161
Asthma	3 (5.1)	4 (7.5)	0.591
Depression	7 (11.9)	10 (18.9)	0.302
Osteoarticular problems	4 (6.8)	6 (11.3)	0.400
Gastric problems	4 (6.8)	5 (9.4)	0.606
Constipation	8 (13.6)	3 (5.7)	0.161
Menopause	11 (26.2)	12 (30.8)	0.601
Body composition			
Body weight (kg)	95.5 ± 11.5	95.4 ± 11.9	0.940
BMI (kg/m^2)	33.9 ± 2.6	34.1 ± 2.2	0.852
BFM (kg)	41.0 ± 7.7	41.4 ± 6.4	0.737
BFM (%)	43.3 ± 6.7	43.6 ± 5.7	0.753
SMM (kg)	30.4 ± 6.1	30.1 ± 6.2	0.777
VFA (cm^2)	195.3 ± 36.3	197.6 ± 21.9	0.731
S/V ratio	0.2 ± 0.1	0.2 ± 0.1	0.523
WHR	1.0 ± 0.1	1.0 ± 0.1	0.656
WC (cm)	99.5 ± 9.8	102.2 ± 9.7	0.162

Characteristics	WLM3P Group (n = 59)	LCD Group (n = 53)	p-value[1]
Demographics			
Blood pressure			
SBP (mm Hg)	123.5 ± 14.4	123.4 ± 10.9	0.948
DBP (mm Hg)	84.4 ± 9.4	84.7 ± 9.0	0.904
Metabolic profile			
Glucose (mg/dL)	83.0 ± 8.6	88.1 ± 10.3	0.008*
HOMA-IR	2.4 (1.9, 3.1)	2.8 (2.0, 3.7)	0.082
Insulin (mIU/L)	12.5 ± 5.1	14.5 ± 7.5	0.092
HbA1 (%)	5.5 ± 0.4	5.6 ± 0.5	0.187
LDL (mg/dL)	112.5 ± 34.6	118.6 ± 28.7	0.318
HDL (mg/dL)	50.2 ± 12.6	53.8 ± 13.3	0.136
TG (mg/dL)	102.0 (77.0, 135.0)	115.0 (83.0, 143.0)	0.276
TG/HDL ratio	2.5 (1.6, 3.0)	2.2 (1.6, 3.1)	0.841
hsCRP (mg/dL)	0.4 (0.2, 0.9)	0.7 (0.2, 1.2)	0.199
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.1	0.517
AST (U/l)	20.0 (17.0, 25.0)	22.0 (18.0, 26.0)	0.420
ALT (U/l)	27.0 (18.0, 41.0)	23.0 (17.0, 37.0)	0.751
GGT (U/l)	22.0 (15.0, 32.0)	19.0 (15.0, 28.0)	0.626
Vitamin D (ng/mL)	19.6 ± 7.6	19.9 ± 6.0	0.867
Magnesium (mg/dL)	2.1 ± 0.1	2.1 ± 0.2	0.998
Sodium (mmol/L)	140.0 ± 1.5	140.3 ± 1.8	0.402
Potassium (mmol/L)	4.4 ± 0.3	4.4 ± 0.3	0.819
Dietary intake			
EI (kcal/day)	2073.3 (1810.7, 2308.1)	2064.5 (1876.2, 2391.4)	0.437
Carbohydrates (%TEI)	39.6 (32.2, 44.9)	39.3 (32.1, 42.9)	0.308
Protein (%TEI)	18.6 (16.9, 21.9)	19.7 (17.3, 22.6)	0.327

Characteristics	WLM3P Group (n = 59)	LCD Group (n = 53)	p-value[1]
Demographics			
Fat (%TEI)	38.1 (32.8, 42.0)	38.0 (34.8, 43.2)	0.461
SFA (%TEI)	14.5 (12.6, 17.3)	14.1 (11.7, 16.0)	0.142
Fiber (g/day)	17.9 (15.0, 23.9)	18.4 (14.9, 22.5)	1.000
Physical activity			
PA, total MET min/week	165.0 (0.0, 462.0)	132.0 (0.0, 297.0)	0.213
≥ 500 MET min/week, n (%)	12 (20.3%)	5 (9.4%)	0.108
Fasting window and sleep habits			
Fasting windows (hours)	11.3 (10.3, 12.0)	11.3 (10.5, 12.1)	0.953
Time in bed (hours/day)	7.9 ± 1.0	7.7 ± 0.8	0.192

Abbreviations: WLM3P, Weight Loss Maintenance 3 Phases Program (Intervention group); LCD, Low-carbohydrate diet (Control group); BMI, Body mass index (calculated as weight in kilograms divided by height in meters squared); BFM, Body fat mass; SMM, Skeletal muscle mass; S/V ratio, Skeletal muscle mass-to-visceral fat area ratio; VFA, Visceral fat area; WC, Waist circumference; WHR, Waist-to-hip ratio; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LDL, Low-density lipoprotein cholesterol; HDL, High-density lipoprotein cholesterol; TG, Triglycerides; TG/HDL ratio, Triglyceride/high-density lipoprotein cholesterol; hsCRP, High sensitivity C-reactive protein; EI, Energy intake; SFA, Saturated fatty acid; PA, Physical activity; MET, Metabolic equivalent; %TEI, % of Total energy intake. Data were presented as number of participants (%), mean ± standard deviation (± sd) for normally distributed variables or the median and interquartile (IQR, 25th-75th percentile) for non-normal distribution variables. [1]p-values were computed with T test for independent samples; Chi-Square test and Mann Whitney test as appropriate, considering the distribution of variables. Differences were statistically significant when *p < 0.05.

3.2. Changes in WL at 6 months (from baseline to 6 months) and 18 months (from baseline to 18 months)

In the complete-case analysis, at 6 months, the WLM3P group achieved a percentage WL of 19.0 ± 5.2%, corresponding to a reduction of 18.1 ± 5.7 kg, compared to 11.9 ± 6.1% and a reduction of 11.5 ± 6.5 kg in the LCD group (n = 46 for each). The estimated treatment difference was − 7.6% (95% CI: −9.9 to − 5.3%; p < 0.001). At 18 months, the WLM3P group (n = 40) had a percentage WL of 15.5 ± 8.3%, resulting in a reduction of 14.8 ± 8.6 kg, while the LCD group (n = 37) achieved a percentage WL of 9.6 ± 8.5% and a reduction of 9.2 ± 8.3 kg. The estimated treatment difference was − 6.1% (95% CI: −9.9 to − 2.3%; p = 0.002) (Table 2 and Supplementary Figure S1). The criterion for clinically significant WL was set at ≥ 5%, which is widely used for meaningful response [5]. In this trial, most participants achieved this benchmark

(at 6 months, 100% in the WLM3P group vs. 93.5% in the LCD group, p = 0.078; and at 18 months, 87.5% in the WLM3P group vs. 75.7% in the LCD group, p = 0.179). Supplementary Figure S2 presents the proportion of participants with a recorded WL of more than 5%, 10%, 15%, and 20% between baseline, 6 months, and 18 months. WLM3P participants were more likely to achieve WL ≥ 10% (6-month: odds ratio [OR] = 41.5 [95% CI: 4.9–383.1]; 18-month: OR = 3.0 [95% CI: 1.1–8.2] and WL ≥ 15% (6-month: OR = 9.9 [95% CI: 3.4–28.8]; 18-month: OR = 4.0 [95 CI 1.4–11.1]). The proportion of participants achieving a WL ≥ 20% was higher in the WLM3P group at 6 months (OR = 5.8 [95% CI: 1.9–17.4]) and at 12-month (OR = 5.0 [95% CI: 1.5–17.1]) (Supplementary Table S2).

Table 2
Changes in outcome measures among completing study participants - comparative analysis at 6, 18 months, and baseline by groups.

Variable	n	WLM3P Group	n	LCD Group	Estimated Treatment Difference (95% CI)	p-value[1]
Body composition						
△ Body weight (Kg)						
6-month	46	-18.1 ± 5.7	46	-11.5 ± 6.6	-7.3 (− 9.7 to − 4.9)	< 0.001*
18-month	40	-14.8 ± 8.6	37	-9.2 ± 8.3	-5.6 (-9.7 to -1.7)	0.006*
△ Body weight (%)						
6-month	46	-19.0 ± 5.2	46	-11.9 ± 6.1	-7.6 (-9.9 to -5.3)	< 0.001*
18-month	40	-15.5 ± 8.3	37	-9.6 ± 8.5	-6.1 (-9.9 to -2.3)	0.002*
△ BMI (kg/m^2)						
6-month	46	-6.5 ± 1.8	46	-4.0 ± 2.2	-2.6 (-3.5 to -1.8)	< 0.001*
18-month	40	-5.3 ± 3.0	37	-3.2 ± 2.8	-2.1 (-3.5 to -0.8)	0.003*
△ BFM (kg)						
6-month	46	-14.9 ± 5.4	46	-9.3 ± 5.8	-6.2 (-8.5 to -3.8)	< 0.001*
18-month	40	-11.2 ± 7.4	37	-6.7 ± 7.2	-4.7 (-8.2 to -1.2)	0.009*
△ BFM (%)						
6-month	46	-9.8 ± 5.4	46	-5.4 ± 4.1	-4.6 (-6.7 to -2.6)	< 0.001*
18-month	40	-6.6 ± 6.2	37	-3.6 ± 5.0	-3.2 (-5.9 to 0.5)	0.023*
△ SMM (kg)						
6-month	46	-2.0 ± 0.9	46	-1.4 ± 1.1	-0.7 (-1.1 to -0.2)	0.003*

Variable	n	WLM3P Group	n	LCD Group	Estimated Treatment Difference (95% CI)	p-value[1]
Body composition						
18-month	40	-2.4 ± 1.4	37	-1.6 ± 1.4	-0.8 (-1.4 to −0.1)	0.028*
△ VFA (cm^2)						
6-month	46	-72.7 ± 28.7	46	-42.7 ± 26.7	-31.2 (-42.9 to-19.5)	< 0.001*
18-month	40	-53.1 ± 38.1	37	-29.8 ± 34.6	-23.3 (-40.7 to -5.8)	0.010*
△ S/V ratio						
6-month	46	0.11 ± 0.13	46	0.06 ± 0.11	0.05 (0.01 to 0.09)	0.022*
18-month	40	0.07 ± 0.11	37	0.04 ± 0.09	0.03 (0.00 to 0.08)	0.296
△ WHR						
6-month	46	-0.09 ± 0.05	46	-0.04 ± 0.05	-0.04 (-0.02 to -0.06)	< 0.001*
18-month	40	-0.07 ± 0.06	37	0.03 ± 0.05	-0.04 (-0.06 to -0.12)	0.004*
△ WC (cm)						
6-month	46	-14.6 ± 5.4	46	-9.6 ± 5.6	-5.7 (-8.1 to -3.4)	< 0.001*
18-month	40	-12.2 ± 7.8	37	-8.8 ± 7.3	-3.8 (-7.3 to -0.1)	0.042*
Blood pressure						
△ SBP (mm Hg)						
6-month	46	-9.5 (-19.5, -2.0)	46	-8.3 (-13.9, -0.5)	-2.3 (-6.7 to 2.1)	0.306
18-month	40	-8.4 (-17.4, -2.1)	37	-6 (-16.0, 2.0)	-1.6 (-6.3 to 3.2)	0.521
△ DPB (mm Hg)						
6-month	46	-7.5 (-11.5, -4.0)	46	-6.0 (-9.0, -2.9)	-3.1 (-5.7 to -0.5)	0.021*

Variable	n	WLM3P Group	n	LCD Group	Estimated Treatment Difference (95% CI)	p-value[1]
Body composition						
18-month	40	-4.0 (-10.4, 0.75)	37	-3.5 (-7.0, 3.3)	-2.8 (-6.3 to 0.7)	0.113
Metabolic profile						
△ Glucose (mg/dL)						
6-month	46	-2.7 ± 7.9	45	-3.1 ± 8.9	-0.1 (-3.5 to 3.3)	0.143
18-month	39	-1.0 (-6, 6)	37	0 (-5.5, 4.5)	-0.4 (-4.0 to 3.1)	0.821
△ Insulin (mIU/L)						
6-month	46	-4.1 (-7.4, -1.5)	45	-4.2 (-6.5, -0.9)	-1.5 (-3.6 to 0.7)	0.174
18-month	39	-4.2 (-7.4, -1.8)	37	-2.5 (-6.4, 1.0)	-2.2 (-4.6 to 0.0)	0.050
△ LDL (mg/dL)						
6-month	46	2.0 (-12.5, 13.0)	45	-4.0 (-16, 8.0)	5.8 (15.1 to − 3.5)	0.222
18-month	39	4.0 (-12.0, 14.0)	37	-10.0 (-21.0, 6.0)	3.8 (13.8 to − 6.3)	0.465
△ HDL (mg/dL)						
6-month	46	8.0 (3.0, 11.0)	45	5.0 (-0.5, 8.5)	3.9 (6.8 to 0.9)	0.010*
18-month	39	10.4 ± 11.4	37	5.3 ± 8.0	6.3 (10.9 to 1.7)	0.007*
△ TG (mg/dL)						
6-month	46	-26.5 (-50.0, -9.8)	43	-25.0 (-64.5, 7.0)	-8.6 (-33.2 to 14.9)	0.473
18-month	39	-25.0 (-49.0, 7.0)	37	-6.0 (-36.0, 16.0)	-30.4 (− 61.2 to 0.4)	0.053
△ TG/HDL ratio						
6-month	46	-0.7 (-1.2, -0.4)	45	-0.7 (-1.5, 0.2)	-0.4 (-1.1 to 0.3)	0.242

Variable	n	WLM3P Group	n	LCD Group	Estimated Treatment Difference (95% CI)	p-value[1]
Body composition						
18-month	39	-0.7 (-1.1, 0.3)	46	-0.3 (-1.1, 0.3)	-1.0 (-1.9 to -0.1)	0.036*
△ hsCRP (mg/dL)						
6-month	46	-0.25 (-0.46, 0.04)	45	-0.25 (-0.46, 0.04)	-0.08 (-0.3 to − 0.1)	0.462
18-month	39	-0.29 (-0.60, 0.02)	37	-0.20 (-0.56, 0.01)	-0.02 (-0.25 to 0.22)	0.873
Dietary intake						
△ EI (kcal/day)						
6-month	46	1313.8 (1167.5, 1406.8)	46	1444.4 (1304.6, 1573.6)	-209.6 (-306.6 to -112.5)	< 0.001*
18-month	40	1465.6 (1357.9, 1647.9)	37	1760.3 (1614.8, 2036.7)	-323.8 (-489.2 to -158.4)	< 0.001*
△Carbohydrates (%TEI)						
6-month	46	16.7 (14.4, 24.6)	46	25.1 (22.1, 28.6)	-6.1 (-9.3 to -2.9)	< 0.001*
18-month	40	27.4 (24.8,32.8)	37	34.4 (30.4, 39.1)	-5.7 (-8.5 to -2.9)	< 0.001*
△Protein (%TEI)						
6-month	46	31.8 (28.6, 34.2)	46	27.0 (24.6, 29.4)	5.9 (8.0 to 3.9)	< 0.001*
18-month	40	27.9 (25.7, 31.1)	37	23.6 (21.0, 26.8)	4.1 (5.9 to 2.2)	< 0.001*
△Fats (%TEI)						
6-month	46	45.6 (42.3, 48.7)	46	44.4 (40.4, 48.9)	0.6 (3.1 to -1.9)	0.661
18-month	40	40.6 (37.4, 43.0)	37	37.4 (34.9, 40.7)	1.8 (4.0 to -0.3)	0.091
△SFA (%TEI)						

Variable	n	WLM3P Group	n	LCD Group	Estimated Treatment Difference (95% CI)	p-value[1]
Body composition						
6-month	46	11.4 (10.5, 13.0)	46	11.7 (10.2, 13.2)	-0.8 (-1.8 to 0.3)	0.159
18-month	40	11.0 (9.3, 11.8)	40	11.1 (9.9, 12.1)	-0.3 (-1.2 to 0.5)	0.441
△Fiber (g/day)						
6-month	46	19.2 (15.5, 21.3)	46	15.1 (12.9, 18.8)	1.9 (4.7 to -0.9)	0.040*
18-month	40	18.9 (16.5, 21.1)	37	18.2 (14.4, 22.6)	-0.2 (-2.6 to 2.2)	0.870
Physical activity						
△PA (total MET min/week)						
6-month	46	594 (288.8, 1235.3)	46	453.8 (1980.0, 813.0)	204 (493.0 to -83.6)	0.164
18-month	40	480 (208.5, 693.0)	37	213.0 (0.0, 720.0)	112.0 (454.0 to -230.3)	0.521
Fasting window						
△Fasting window (h/day)						
6-month	46	13.5 (12.4, 15.1)	46	11.4 (11.0, 12.0)	2.4 (2.9 to 1.9)	< 0.001*
18-month	40	13.1 (12.0, 13.7)	37	11.3 (11.1,12.0)	1.4 (2.0 to 0.9)	< 0.001*

Abbreviations: WLM3P, Weight Loss Maintenance 3 Phases Program (Intervention group); LCD, Low-carbohydrate diet (Control group); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BFM, Body Fat Mass; SMM, Skeletal muscle mass; S/V ratio, Skeletal muscle mass-to-visceral fat area ratio; VFA, Visceral fat area; WHR, Waist-to-hip ratio; WC, Waist circumference; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; TG/HDL ratio, Triglyceride/high-Density Lipoprotein Cholesterol; hsCRP, high sensitivity C-reactive protein; EI, Energy Intake; SFA, saturated fatty acid; PA, physical activity, MET, metabolic equivalent; %TEI, % of total energy intake. All data were presented as mean ± standard deviation (± sd) for normally distributed variables or the median and interquartile (IQR, 25th-75th percentile) for non-normal distribution variables. Change scores from baseline were represented by "Δ" in the table. [1]p-values were computed with a linear regression model considering as confounders: age, sex, body mass index, and baseline glucose (used since differences were observed at baseline). Differences were statistically significant when *p < 0.05.

3.3. Changes in body composition and metabolic profile (from baseline to 18 months)

Between baseline and 18 months, the WLM3P group showed a greater reduction in BMI compared to the LCD group (adjusted difference − 2.1 kg/m^2; 95% CI: -3.5 to -0.8 kg/m^2). The same trend was observed for other parameters, such as the percentage of BFM (–3.2%; 95% CI: -5.9 to − 0.5%), VFA (–23.3 cm^2; 95% CI:-40.7 to -5.8 cm^2), WC (–3.8 cm; 95% CI:-7.3 to -0.1 cm), WHR (–0.04; 95% CI:-0.06 to -0.12), HDL (6.3 mg/dL; 95% CI: 10.9 to 1.7 mg/dL), and TG/HDL ratio (–1.0; 95% CI: -1.9 to − 0.1). Both groups experienced a significant loss of SMM over the 6- and 18-months periods ($p \leq 0.001$). However, the reduction in SMM in the WLM3P group was greater than the one observed in the LCD group (6-month: -0.7 kg; 95% CI: -1.1 to -0.2 kg; 18-month: -0.8 kg; 95% CI: -1.4 to -0.1 kg). Nevertheless, despite this absolute reduction in SMM, the S/V ratio increased in both groups, with a significant difference observed at 6 months favoring WLM3P intervention (0.051; 95% CI: 0.007 to 0.094) (Table 2). The WLM3P showed a greater reduction in mean diastolic blood pressure at 6 months (-3.1 mmHg; 95% CI: -5.7 to 0.5 mmHg), without differences between groups at the end of the study. The vitamin D blood levels increased more after WL period in the WLM3 group ($p = 0.029$) compared to the control group. At 18 months, median creatinine concentrations were significantly different between groups but without clinical relevance: WLM3P group: 0.70 (0.60, 0.79) mg/dL; LCD group: 0.78 (0.68, 0.88) mg/dL (Supplementary Table S3). No significant differences were found for other biochemical parameters and systolic blood pressure values (Table 2 and supplementary Table S3). Among the participants who were previously on treatment for hypertension (n = 19; 17%), n = 6 (7.8%) discontinued the antihypertensive medications [(WLM3P group: 4 (10%); LCD group: 2 (5.4%)] and n = 4 (5.2%) reduced the dose and/or number of antihypertensive medications [(WLM3P group: 1(2.5%); LCD group: 3 (8.1%)] at 18 months.

3.4. Changes in body composition between WL phase and maintenance phase (from 6 to 18 months)

Adjusted weight regain data from the end of the WL intervention to the end of the maintenance period (6–18 months) are displayed in Table 3. There was no significant difference in weight regain between the groups (WLM3P group: 4.3 ± 5.8% and LCD group: 3.5 ± 4.8%, $p = 0.541$). Also, there was no significant group difference in regain of BFM, VFA, SMM, WC, and WRH between 6 and 18 months (Table 3).

Table 3
Body composition changes during the weight maintenance phase (6 to 18 months) among completing study participants, by groups.

Variable	WLM3P Group (n = 39)	LCD Group (n = 37)	Estimated Treatment Difference (95% CI)	p-value[1]
△ Body weight (kg)	4.1 ± 6.1	3.5 ± 4.9	1.2 (1.5 to − 3.7)	0.381
△ Body weight (%)	4.3 ± 5.8	3.5 ± 4.8	1.2 (1.4 to − 3.7)	0.357
△ BFM (kg)	4.7 ± 5.3	3.8 ± 4.7	1.3 (3.6 to − 1.0)	0.254
△ BFM (%)	3.9 ± 3.7	2.6 ± 3.4	1.4 (3.1 to − 0.2)	0.085
△ SMM (kg)	-0.4 ± 1.3	-0.1 ± 0.9	-0.2 (0.3 to − 0.7)	0.384
△ VFA (cm^2)	24.3 ± 25.1	18.0 ± 21.1	7.6 (18.3 to − 3.1)	0.165
△ S/V ratio	0.05 ± 0.09	0.03 ± 0.08	-0.03 (0.01 to − 0.07)	0.141
△ WHR	0.03 ± 0.04	0.02 ± 0.03	0.01 (0.03 to − 0.00)	0.080
△ WC (cm)	3.1 ± 5.3	1.9 ± 4.3	1.6 (3.8 to − 0.7)	0.169

Abbreviations: WLM3P, Weight Loss Maintenance 3 Phases Program (Intervention group); LCD, Low-carbohydrate diet (Control group); BFM, Body Fat Mass; SMM, Skeletal muscle mass; S/V, ratio, Skeletal muscle mass-to-visceral fat area ratio; VFA, Visceral fat area; WHR, Waist-to-hip ratio; WC, Waist circumference. Change scores are represented by "△" in the table. All data were presented as mean ± standard deviation (± sd). [1]p-values were computed with a linear regression model considering as confounders: age, sex, body mass index, and baseline glucose (used since differences were observed at baseline). Differences were statistically significant when *p < 0.05.

3.5. Dietary intake and physical activity

Based on the analysis of the dietary intake data, no significant differences were observed between the WLM3P and LCD groups regarding energy intake (kcal/d), macronutrient composition and fiber at baseline (Table 2). Participants in the WLM3P group displayed a greater reduction in energy intake compared to the LCD group (6-month: −209.6 kcal/day; 95% CI: −306.6 to − 112.5 kcal/day; 18-month: −323.8 kcal/day; 95% CI: − 489.2 to -158.4 kcal/day). As expected, the WLM3P group exhibited a significant reduction in %TEI from carbohydrate consumption (6-month: 16.7% in WLM3P| 25.1% in LCD; 18-month: 27.4% in WLM3P| 34.4% in LCD), along with a higher %TEI from protein compared to the LCD group at both time points (6-month: 31.8% in WLM3P|27.0% in LCD; 18-month, 27.9% in WLM3P| 23.6% in LCD). No differences were observed in %TEI from fat and saturated fat consumption between groups at

any time point. It is worth noting that both groups fell short of the recommended doses of 25 g/day of fiber (Table 2).

Regarding to physical activity, it was found that at baseline, 79.7% (n = 47) participants in the WLM3P group and 90.6% (n = 48) in the LCD group failed to achieve the recommended physical activity level of ≥ 500 MET-min/week (p = 0.108). The range of physical activity level was 0–462 MET-min/week in the WLM3P group and 0–297 MET-min/week in the LCD group (p = 0.213). At 6 months, participants in both groups displayed an increase in physical activity [(58.7% (n = 27) in WLM3P and 45.7% (n = 21) in LCD reported a physical activity level ≥ 500 MET-min/week, p = 0.210)]. At 18 months, 52.5% and 62.2% failed to achieve the recommended physical activity level of ≥ 500 MET-min/week in each group, respectively (p = 0.392).

3.6. Fasting window and sleep habits

As anticipated, the WLM3P group exhibited longer median durations of overnight fasting compared to the LCD group (6-month: 13.5 hours in WLM3P|11.4 hours in LCD; 18-month: 13.1 hours in WLM3P; 11.3 hours in LCD) (Table 2). There were no changes in sleep duration from the beginning to the end of the study in either group (supplementary Table S3).

3.7. Compliance and withdrawal

The level of adherence among the patients was high. On average, after 18 months, participants in the WLM3P group attended 88.3 ± 7.9% of the sessions (32 out of 36 sessions), while participants in the LCD group attended 85.4 ± 12.4% of the sessions (15 out of 18 sessions). Within the WLM3P group, during the 6 months WL phase, the reported adherence to dietary supplements averaged at 78.3 ± 14.5%. A total of 31% (n = 35) of participants withdrew from the study, with a similar proportion in both groups [(32.2% (n = 19) in WLM3P and 30.2% (n = 16) in LCD; p = 0.818)]. The majority of participants dropped out within the first 6 months (17.9% (n = 20); (28.2% (n = 13) |WLM3P, 15.2% (n = 7)|LCD; p = 0.223). The dropout pattern was analyzed by comparing the baseline characteristics of completers and non-completers, and our results showed no significant differences between the two groups in relation to body composition and biochemical parameters (supplementary Table S4). Importantly, none of the participants withdrew due to adverse events.

3.8. Adverse effects

In both groups, adverse effects occurred during the initial 6 months of the WL phase, with a higher prevalence observed in the WLM3P group (p = 0.020). These adverse effects were generally moderate and transient. The most reported was constipation (Table 4 presents a detailed report of adverse effects). However, it is worth mentioning that at baseline, 13.6% (n = 8) of the WLM3P participants reported constipation (Table 1). The WLM3P group, which included dietary supplements with diuretic characteristics during the WL phase, did not experience significant fluctuations in serum potassium and sodium levels (supplementary Table S3).

Table 4
Prevalence of adverse effects at 1 and 6 months in both groups.

Adverse effects	Month	WLM3P Group	LCD Group	p-value[1]
Yes, n (%)	1	20 (35.7)	11 (20.8)	0.084
	6	11 (23.9)	3 (6.5)	0.020*
Constipation, n (%)	1	15 (26.8)	4 (7.5)	0.008*
	6	5 (10.8)	2 (4.3)	0.238
Fatigue, n (%)	1	5 (8.9)	4(7.5)	0.793
	6	-	-	-
Headaches, n (%)	1	2 (3.6)	2 (3.8)	0.955
	6	-	-	-
Irritability, n (%)	1	0 (0)	2 (3.8)	0.142
	6	-	-	-
Diarrhea, n (%)	1	0 (0)	1 (1.9)	0.302
	6	-	-	-
Nauseas, n (%)	1	1 (1.7)	0 (0)	0.155
	6	-	-	-
Hair loss, n (%)	1	-	-	-
	6	4 (8.7)	1 (2.2)	0.168

Data are the number of participants (%). Abbreviations: WLM3P, Weight Loss Maintenance 3 Phases Program (Intervention group); LCD, Low-carbohydrate diet (Control group); [1]p-values: Chi-Square test. Differences were statistically significant when *p < 0.05.

4. Discussion

The rising prevalence of obesity emphasizes the urgent need for effective weight management strategies. Alternatives to conventional methods, such as diet alone, diet and exercise, exercise alone, meal replacements, very-low-energy diets, pharmacotherapy, and advice alone, are needed [5]. Despite the

availability of commercial weight management programs, most of the interventions used in previous studies were not intensive and multicomponent, and their follow-up periods were relatively short to adequately demonstrate long-term weight loss [5, 10].

This study evaluated the effectiveness of a multicomponent behavioral weight management program, the WLM3P, in achieving and maintaining a clinically significant WL (≥ 5%) compared to a LCD. The primary findings from this 18-month study demonstrate that both WLM3P and LCD groups were successful in achieving and maintaining clinically significant WL ≥ 5%. Moreover, a higher proportion of participants in the WLM3P group reached higher %WL targets, such as WL ≥ 10% and 15%. These higher %WL targets have been associated with additional clinical benefits and are frequently more desirable for clinical purposes[5, 6].

The %WL and the proportion of participants losing 5% of their initial body weight observed in this study were higher than those reported in others intensive lifestyle interventions at 12-month (mean of WL = 8% and WL ≥ 5% = 66.3–70.2%)[8]. The %WL results achieved in our study are more comparable to the results reported in clinical research protocols that use pharmacotherapy for obesity treatment, which typically show %WL in the range of 6.5–14.9% [8]. Nevertheless, all these interventions are typically characterized by high attrition rates and weight relapse[5][10] [8]. In our study, from months 6 to 18, participants in both WLM3P and LCD groups experienced weight regain (< 5%), with no significant difference between the two groups. This resulted in net losses of 15.5% and 9.6%, respectively. Maintaining WL and preventing weight regain is critical, as it has a potential negative impact on body composition and cardiometabolic health[5, 6].

The 18 months intervention of WLM3P resulted in significant reductions in BMI, BFM, VFA, WHR, and WC, as well as improvements in HDL cholesterol and TG/HDL ratio (atherogenic index) compared with LCD (Fig. 2). It is critical to derive WL primarily from BFM as excess adiposity is highly associated with other metabolic diseases [1]. Nevertheless, some studies have shown that WL is accompanied by the loss of tissue from the fat-free compartment, particularly SMM [32]. Low SMM and high VFA are known to be associated with atherosclerosis, cardiovascular diseases, sarcopenic obesity, insulin resistance and nonalcoholic fatty liver [33, 34]. From baseline to 6 months, the S/V ratio, which captures changes in SMM and VFA, showed a significant improvement in the WLM3P group compared to LCD. These findings indicate that WLM3P can be more effective than LCD in maintaining a metabolically healthy state [33, 34].

Greater WL has been associated with improved lipid profile [5, 6], including increased levels of HDL cholesterol and reduced TG/HDL ratio, which are linked to lower risk of cardiovascular disease [35]. The WLM3P group showed a greater increase in HDL cholesterol in comparison with the control group and others popular diet programs [11]. Diet composition is an important determinant of HDL and TG metabolism [36]. According to a network meta-analysis and nutritional geometry approach, a low-carbohydrate/high-protein diet (comprising 30%TEI from protein, ≤ 40% from carbohydrate, and ≥ 35% from fat) similar to those prescribed to the WLM3P group, particularly during phase 3 (weight

maintenance) is identified as the most effective in increasing HDL cholesterol and reducing TG [36] which might explain the superior benefits in HDL cholesterol levels and TG/HDL ratio obtained in this group.

Regarding to improvements in blood pressure, according to a systematic review and meta-analysis, WL of 5%-10% is expected to lead to larger reductions in SBP of 4.9 mmHg and DBP of 2.6 mmHg over 6 to 12 months[37]. A similar degree of reduction in SBP and DBP was observed for a superior WL in both groups of our study, possibly due to the mixed-status hypertension of participants (both hypertensive and non-hypertensive).

From a clinical perspective, the positive outcomes observed in both groups might be attributed to a number of factors, included: i) long intervention period that may help participants established new lifestyle habits [5], ii) high emphasis on diet quality[38], iii) reduction in TEI during WL [5], iv) dietary macronutrient composition [(a high-protein diet is reported to be effective in inducing WL, BF reduction, preservation of lean mass [15, 16] and lower weight regain in the short term (3–12 months)] [39], v) high attendance rates to sessions (superior than 60.5% reported by others WL intervention [40]), vi) adequate sleep duration (≈ 8 h that has been linked to better WL outcomes)[25], and vii) increase in the proportion of participants that achieve the recommended physical activity level of ≥ 500 MET-min/week compared to baseline.

Other components of the WLM3P program may also have positively influenced weight management. The WLM3P is a high-intensity intervention (24 sessions in 6 months) that can provide numerous benefits for WL, including personalized guidance, support, goal setting, nutritional education, and long-term success [5, 6]. Also, integrate TRE as a strategy. Pamela et al.[41] found that participants with obesity who completed 8 weeks of a 14:10 TRE schedule combined with a commercial WL program had a greater reduction in body weight compared to a 12:12 TRE schedule. Furthermore, a systematic review and meta-analysis indicated that TRE combined with calorie restriction effectively reduced body weight, BFM, and WC[20]. Prolonged nightly fasting (WL phase: median 13.5 hours and weight maintenance phase: median 13.1 hours) promotes a metabolic switch, where the primary source of energy shifts from glucose to fat and ketones, potentially improving anthropometric measurements and cardiometabolic health [20, 42]. Given the continued high interest in strategies for successful weight management, WLM3P program uses dietary supplements, vitamins, and minerals supplements, to prevent potential micronutrient deficiency[21, 22] and, bioactive compounds (i.e.: L-Carnitine, green tea, green tea, chromium) that can impact on satiety, lipid absorption and fatty acids beta-oxidation. The safety and efficacy of WL programs that use supplements as adjuncts have been poorly evaluated in randomized controlled trials[21, 22] making it difficult for health professionals to refer patients to evidence-based programs due to a lack of understanding of the role of supplements on obesity treatment.

In addition, WLM3P program has a mobile/web platform with visual progress charts, dietary prescriptions, and goals definitions, setting to enhance therapeutic adherence [24]. Several studies have

explored the use of digital health solutions for obesity and have shown promising results in promoting eating behavior change and WL [23].

In our study, no serious adverse events were reported, and constipation was the most common adverse event, but at a lower rate than reported in other weight loss programs [10]. When considering a weight management program that includes dietary supplements with diuretic characteristics, it is important to monitor potassium and sodium levels[43]. These electrolytes balance was not affected by the WLM3P intervention (supplementary Table S3).

The withdrawal rate at 18 months in our study (31%) was slightly below the average for weight loss trials at 1 year (37%) [44]. One of the key strengths of our study is the extended period (18 months) of this randomized controlled trial, which allowed us to gather comprehensive and detailed information on weight changes across the study duration. However, it is important to acknowledge the limitations of this study. First, the small sample size might have limited the statistical power, primarily focusing on detecting differences in weight change between the two groups rather than secondary outcomes. Second, due to the study design, we are unable to distinguish between the individual components' effects of the WML3P, nor to analyze their interactions. Further research is needed to understand how each of the 7 components of WLM3P contributes and whether they have synergistic or additive effects on weight management. Third, the control group in our study received active treatment with weight loss and weight maintenance-specific feedback. This might have influenced the outcomes, as a high percentage of participants in both groups achieved WL of $\geq$ 5%. Fourth, we acknowledge that using self-reported questionnaires and dietary records for assessing food intake have limitations. Participants were informed to do written annotations and to take photos of daily meals (food and beverages) during the diet recording days, using measuring cups, spoons, and home scales. Food diaries were reviewed using a photographic manual for food quantification [45]. Despite implementing these strategies, there may still be biases and errors in the data collected. Future research with larger sample sizes is needed to obtain more robust and conclusive results.

Our trial demonstrated that the WLM3P program was highly effective in helping adults with obesity achieve significant and sustained weight loss. The WLM3P resulted in a mean weight loss of 15.5%, with a large proportion of participants (87.5%) reaching the clinically significant milestone of 5% weight loss at the 18 months mark. Notably, the WLM3P program outperformed the LCD group in terms of achieving higher weight loss targets of 10% and 15%, as well as providing additional clinical benefits such as reducing BMI, body fat mass, visceral fat area, waist-to-hip ratio, and TG/HDL ratio, while increasing HDL levels. These improvements have important implications for the management of obesity-related metabolic disorders. Although our study did not specifically isolate the effects of individual program components, it provided valuable evidence of the overall efficacy of multicomponent behavioral weight management programs. These findings contribute to the existing knowledge base and emphasize the potential of multicomponent behavioral weight management programs to address the growing obesity epidemic.

Declarations

Data Availability Statement: The full data sets generated during and/or analyzed during the current study are not publicly available because the ethics committee only allowed the use of the data in the context of the present research project; however, anonymized partial data sets or summaries of the data are available from the corresponding author on reasonable request.

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Ethical Approval: This trial was registered at clinical trials.gov under the identifier NCT04192357. The recruitment and data collection of this study have already been completed. The study was approved by the Ethics Committee of the NOVA Medical School (Lisbon, Portugal) (CEFCM Approval Number: 108/2018) and was registered at www.clinicaltrials.gov (NCT04192357) before participants’ recruitment. All participants provided written informed consent in accordance with the principles of the Declaration of Helsinki. Written informed consent has been obtained from the patients to publish this paper.

Competing Interests: Vanessa Pereira and Filipa Cortez work at Farmodiética S.A., one of the study sponsors. The sponsor provided support in the form of salaries for the author (Vanessa Pereira) and research materials but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the paper. The other researchers do not have any relationship with this sponsor.

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Figures

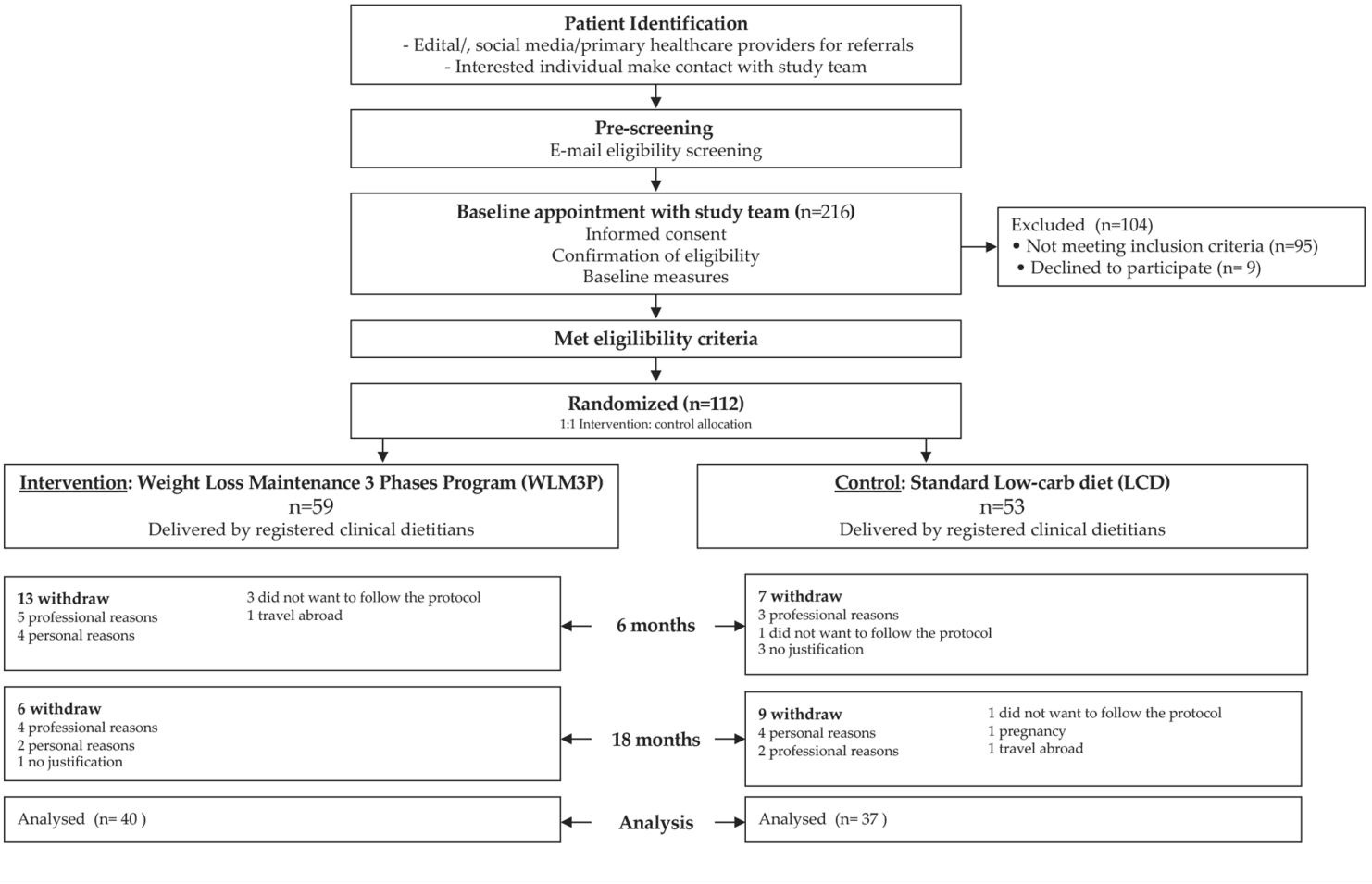

Figure 1

Flow diagram of the study participants.

Abbreviations: WLM3P, Weight Loss Maintenance 3 Phases Program (Intervention group); LCD, Low-carbohydrate diet (Control group).

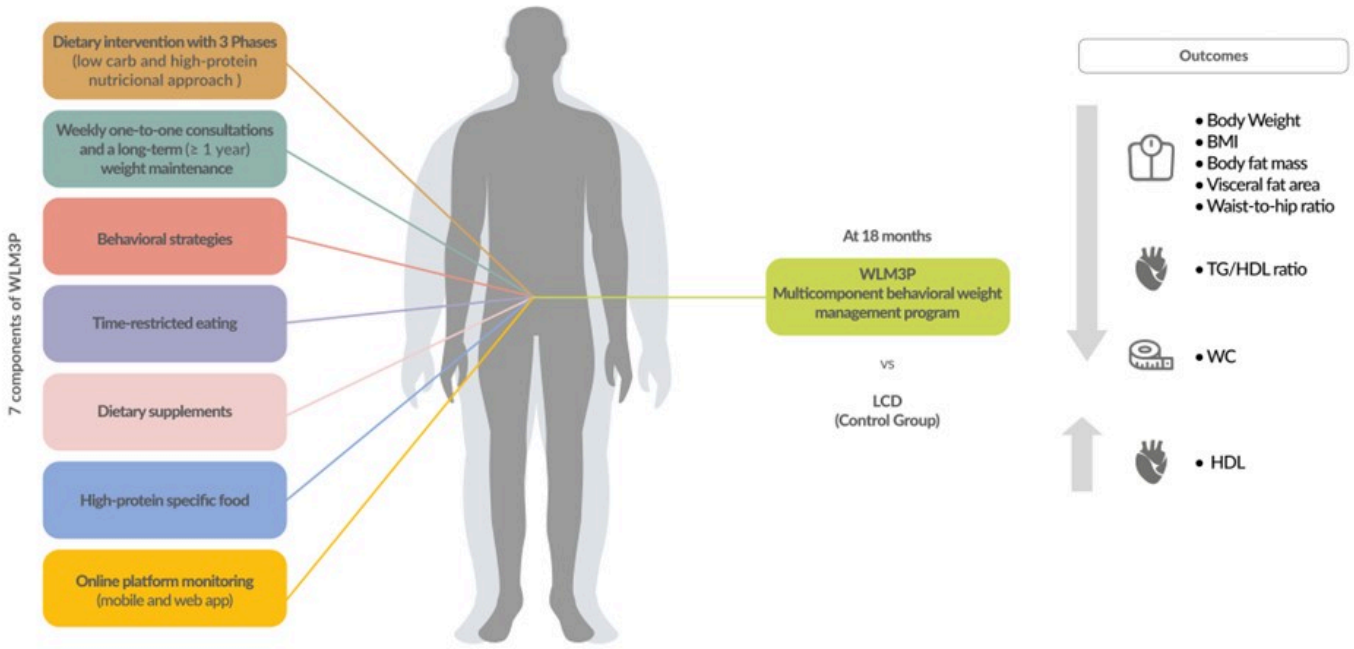

Figure 2

WLM3P group results vs LCD group. Abbreviations: WLM3P, Weight Loss Maintenance 3 Phases Program (Intervention group); LCD, Low-carbohydrate diet (Control group)

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